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Synthesis and Reactivity of 3-(Benzothiazol-2-yl)-3-oxopropanenitrile

Ahmad M. Farag*, Kamal M. Dawood and Zaghloul E. Kandeel

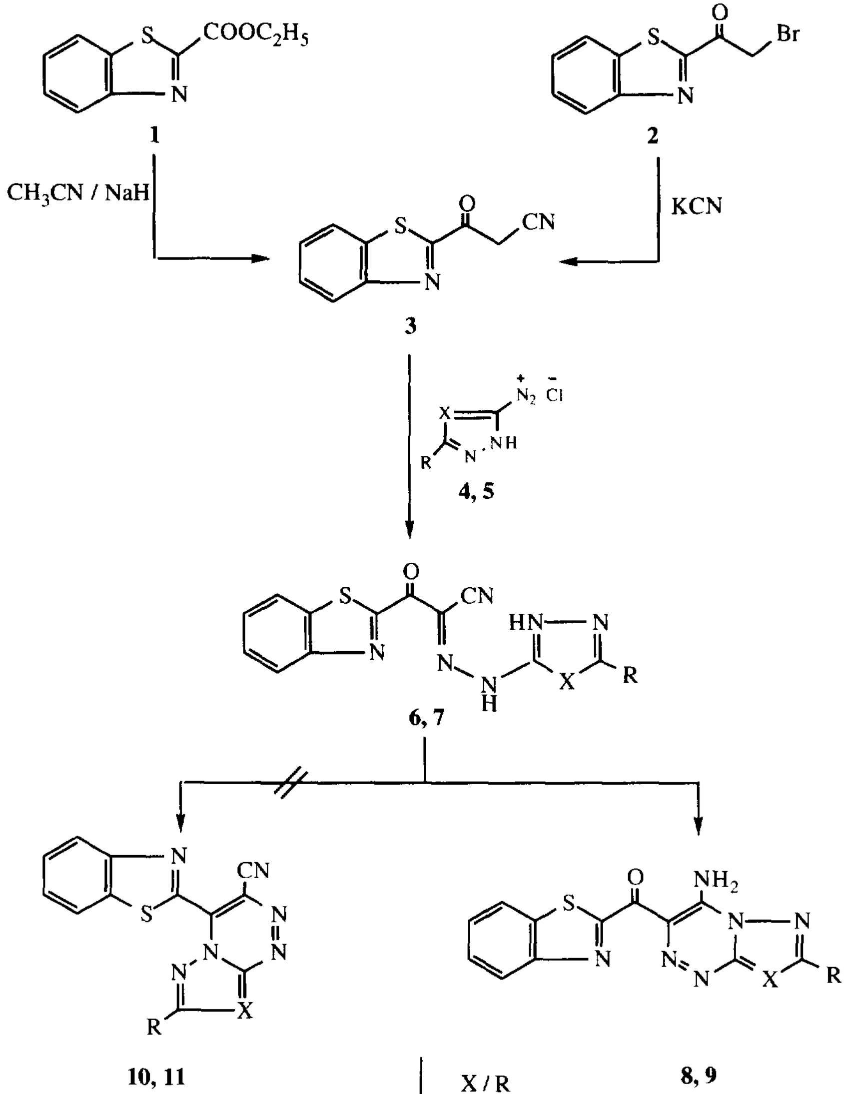
Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt.

***Abstract:*:** The versatile, hitherto unreported 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**3**) was prepared by two convenient routes : either by the reaction of ethyl 2-benzothiazolecarboxylate (**1**) with acetonitrile in the presence of sodium hydride or by treatment of 2-bromoacetylbenzothiazole (**2**) with potassium cyanide . Reaction of **3** with heterocyclic diazonium salts furnished the corresponding hydrazones **6, 7** and **13,** respectively. The latter products underwent intramolecular cyclization into the corresponding pyrazolo[5,1-c]-1,2,4-triazine, 1,2,4-triazolo[5,1-c]-1,2,4-triazine and 1,2,4-triazolo[4,3-a]benzimidazole derivatives **8, 9** and **14,** respectively, upon boiling in pyridine. Compound **3** coupled also with diazotized aromatic amines and gave the corresponding arylhydrazones **16a-c** which undergo cyclocondensation with hydrazine and phenylhydrazine to afford the pyrazole derivatives **17a-c** and **18a-c**, respectively. Cyclocondensation of compound **3** with hydrazine derivatives afforded the corresponding aminopyrazoles **19** and **20,** respectively in good yields.

As part of our programme aimed at developing new approaches for the synthesis of fused ring systems with bridgehead nitrogen atoms[1,2], we report here the synthesis of the versatile, hitherto unreported 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**3**) and its utility as building block in the synthesis of several new heterocycles in which the benzothiazole moiety is incorporated.

Thus, when ethyl 2-benzothiazolecarboxylate (**1**) was treated with acetonitrile in the presence of sodium hydride in refluxing benzene it afforded the novel 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**3**) (Scheme 1). Compound **3** was also prepared by reaction of 2-bromoacetylbenzothiazole (**2**) with ethanolic potassium cyanide solution. The structure of compound **3** was established on the basis of its elemental analyses and spectral data. Its ^{1}H NMR spectrum displayed a singlet signal at δ 4.45 ppm characteristic for active methylene protons whereas its IR spectrum revealed two absorption bands at 2265 and 1719 cm^{-1} due to nitrile and carbonyl functions, respectively.

Treatment of 3-oxopropanenitrile **3** with 3-phenylpyrazole-5-diazonium salt **4** in cold ethanol buffered with sodium acetate furnished a red-coloured product identified as 3-(benzothiazol-2-yl)-3-oxo-2-(3-phenyl-1H-pyrazol-5-ylhydrazono)propanenitrile (**6**) on the basis of its elemental analyses and spectral data. For example, the IR spectrum of **6** showed four absorption bands at 3340, 3194, 2205 and 1659 cm^{-1} assignable to



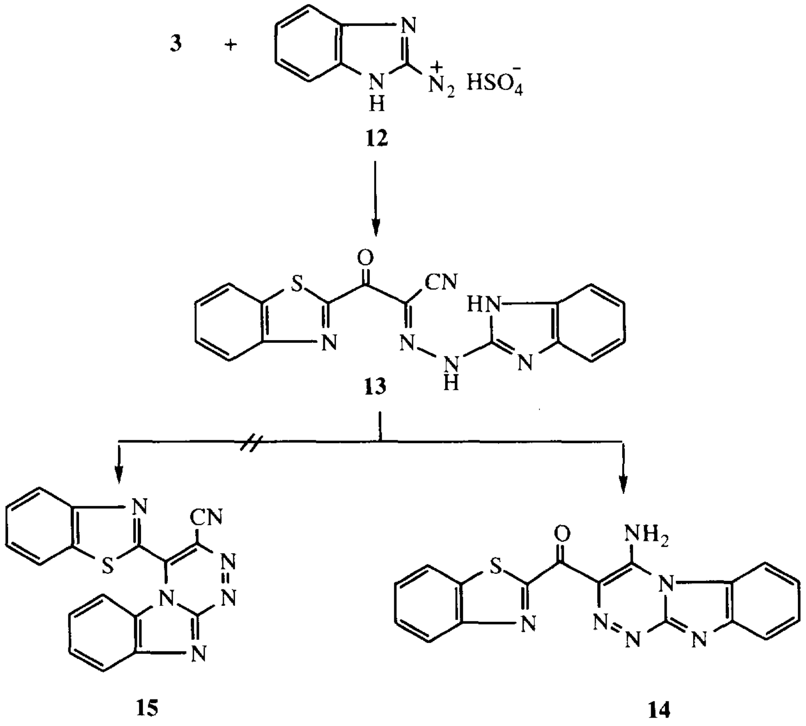
	X / R
4, 6, 8, 10	CH / Ph
5, 7, 9, 11	N / H

Scheme 1

2NH, CN and CO groups, respectively. The latter hydrazone underwent intramolecular cyclization when boiled in pyridine and afforded a pale yellow product. On the basis of elemental analyses and spectral data, the structure of the reaction product was established as 4-amino-3-(benzothiazol-2-yl)carbonyl-7-phenylpyrazolo[5,1-c]-1,2,4-triazine (**8**). Thus, the appearance of NH_2 and CO absorption bands at 3351, 3199 and 1641 cm^{-1}, respectively, and the lack of CN absorption band in the IR spectrum of the reaction product corroborated the assigned structure **8** and ruled out the other possible structure **10** as depicted in scheme 1.

In a similar manner, when **3** was treated with 1,2,4-triazole-5-diazonium salt **5**, the corresponding hydrazone **7** was obtained in high yield. The latter product undergoes intramolecular cyclization when refluxed with pyridine to afford the 1,2,4-triazolo[5,1-c]-1,2,4-triazine structure **9** and not the other possible structure **11**. Both of structure **7** and **9** were assigned on the basis of their elemental and spectral analyses (see Experimental part).

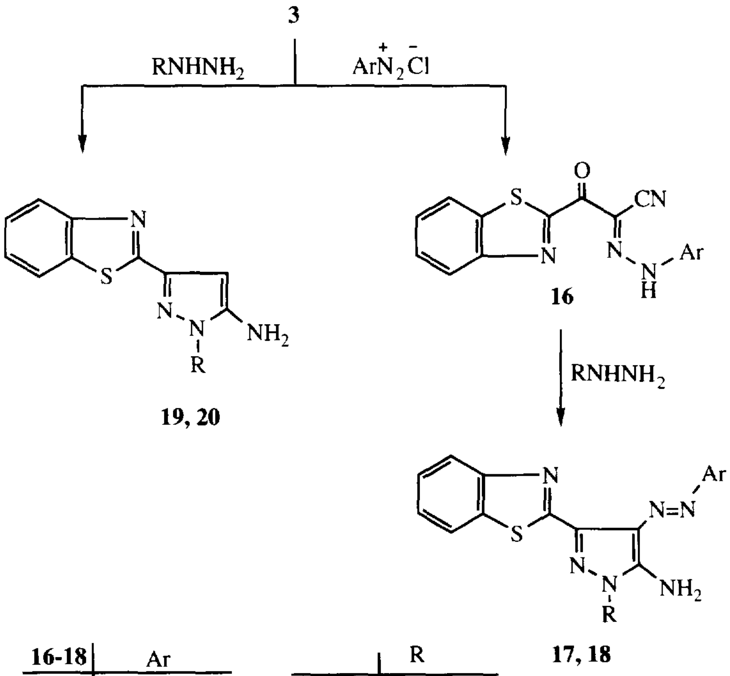
Similar to its behaviour towards **4** and **5**, compound **3** coupled also with 1H-benzimidazole-2-diazonium salt **12** to afford the corresponding hydrazone **13** in high yield. The latter hydrazone was readily cyclized intramolecularly when heated in pyridine to give one product identified as 4-amino-3-(benzothiazol-2-yl)carbonyl-1,2,4-triazino[4,3-a]benzimidazole (**14**) (Scheme 2). The other possible structure **15** was readily eliminated



Scheme 2

for the reaction products on the basis of spectral data. Thus, the appearance of absorption bands corresponding to amino and carbonyl groups at 3300, 3135 and 1652 cm^{-1}, respectively, and the lack of nitrile absorption in the IR spectrum of the reaction product supported the assigned structure **14** and discarded the other possible structure **15**.

Reactions of **3** with aromatic diazonium salts were also invistigated. Thus, treatment of **3** with diazotized aromatic amines in cold ethanol in the presence of sodium acetate at 0-5°C afforded the corresponding hydrazones **16a-c** (Scheme 3). The ^1H NMR spectrum of **16b**, for example, displayed besides an aromatic multiplet at δ 7.2-8.4 ppm, singlet signals at δ 2.35 and 13.35 ppm corresponding to methyl and hydrazone NH protons, respectively. Also, the IR spectra showed, in each case, absorption bands arround 3250, 2220 and 1665 cm^{-1} due to NH, CN and CO groups, respectively. Treatment of the hydrazones **16a-c** with hydrazine hydrate and with phenylhydrazine in refluxing ethanol afforded the corresponding arylazopyrazoles **17a-c** and **18a-c,** respectively. The structures of the latter products were established on the basis of their elemental analyses and spectral data. Thus, the IR spectra of **17a-c** showed, in each case, the absence of nitrile and



16-18	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4

	R
17, 19	H
18, 20	C_6H_5

Scheme 3

carbonyl bands near 2200 and 1660 cm^{-1}, respectively, and revealed the appearance of three bands in the region 3450-3160 cm^{-1} due to NH and NH_2 groups. The IR spectra of **18a-c** exhibited only two bands near 3460 and 3300 cm^{-1} due to NH_2 group.

Compound **3** reacts also with hydrazine hydrate and with phenylhydrazine in refluxing ethanol to afford the corresponding 5-amino-3-(benzothiazol-2-yl)-1H-pyrazole (**19**) and 5-amino-3-(benzothiazol-2-yl)-1-phenylpyrazole (**20**), respectively (Scheme 3), as established from their elemental analyses and spectral data. For example, the IR spectrum of **19** showed three absorption bands in the region 3400-3150 cm^{-1} due to NH and NH_2 groups, whereas the IR spectrum of **20** showed only two bands at 3373 and 3276 cm^{-1} due to NH_2 group.

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide on a Pye-Unicam SP 3-300 infrared spectrophotometer. The ^1H NMR spectra were recorded in deuterated chloroform or DMSO-d_6 on a Varian Gemini 200 NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer at 70 ev. Microanalyses were carried out at the Microanalytical Center, University of Cairo, Giza, Egypt. Ethyl 2-benzothiazolecarboxylate **1**[3], 2-bromoacetylbenzothiazole **2**[4] and heterocyclic diazonium salts **4**[5], **5**, **12**[6] were prepared according to literature procedures.

3-(Benzothiazol-2-yl)-3-oxopropanenitrile (3):

Route A :

To a mixture of ethyl 2-benzothiazolecarboxylate (**1**) (10.35 g, 50 mmol) and acetonitrile (2.7 ml, 50 mmol) in dry benzene (200 ml) and dimethylformamide (10 ml) was added sodium hydride (1.2 g , 85%). The reaction mixture was refluxed for 4h, then allowed to cool. The solid that precipitated was collected, washed with ether and dried. The product was dissolved in water and the resulting solution was treated with concentrated hydrochloric acid untill it becomes neutral. The precipitated product was collected, washed with water, dried and finally recrystallized from toluene / petroleum ether (60/80°C) to afford 7.6 g (75% yield) of **3**; mp 151-2°C; IR (KBr) ν 2265 (C≡N), 1719 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.45 (s, 2H), 7.58-8.25 (m 4H)) ppm; (Calcd. for $C_{10}H_6N_2OS$: C, 59.38; H, 2.99; N, 13.85; S, 15.85. Found: C, 59.51; H, 3.16; N, 13.50; S, 15.72).

Route B:

To a solution of 2-bromoacetylbenzothiazole (**2**) (5.12 g, 20 mmol) in absolute ethanol (30 ml) was added a solution of potassium cyanide (1.3 g, 20 mmol in 5 ml water) with stirring. The reaction mixture was stirred at room temperature for further 4h, then diluted with water. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from toluene / petroleum ether (60/80°C) to afford 2.7 g

(67% yield) of compound **3** identical in all respects (mp., mixed mp. and spectral data) with that obtained by route A above.

Reactions of 3 with heterocyclic diazonium salts 4, 5 and 12.

General procedure:

To a cold solution of 3-oxopropanenitrile **3** (0.404 g, 2 mmol) in ethanol (50 ml) was added the appropriate heterocyclic diazonium salt **4, 5** or **12** (2 mmol) portionwise with stirring at 0-5°C over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4h, then kept in an ice-chest for 12h, and finally diluted with water. The precipitated solid was collected, washed with water, dried and finally recrystallized from dioxane to afford the corresponding hydrazones **6, 7** and **13**, respectively.

6 : Yield (78%); mp. 260-2°C; IR (KBr) ν 3340, 3194 (2 NH), 2205 (C≡N), 1659 (C=O), 1609 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 6.58 (s, 1H, pyrazole H-4), 7.36-8.30 (m, 9H), 9.8 (br., 1H), 11.0 (br., 1H); (Calcd. for $C_{19}H_{12}N_6OS$: C, 61.27; H, 3.24; N, 22.56; S, 8.60. Found : C, 61.30; H, 3.16; N, 22.21; S, 8.57) .

7 : Yield (71%); mp. 271-3°C; IR (KBr) ν 3433, 3247 (2 NH), 2216 (C≡N), 1660 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 6.22 (s, 1H, triazole H-5), 7.24-8.30 (m, 4H), 10.0 (br., 1H), 10.68 (br., 1H) ppm; (Calcd. for $C_{12}H_7N_7OS$: C, 48.47; H, 2.37; N, 32.98; S, 10.78. Found : C, 48.23; H, 2.40; N, 32.66; S, 10.70) .**13**: Yield (83%); mp. 274-6°C; IR (KBr) ν 3273, 3171 (2 NH), 2208 (C≡N), 1630 (C=O), 1605 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 7.2-8.26 (m, 8H), 9.8 (br., 1H), 11.35 (br., 1H) ppm; (Calcd. for $C_{17}H_{10}N_6OS$: C, 58.94; H, 2.91; N, 24.26; S, 9.25. Found : C, 59.06; H, 2.75; N, 23.89; S, 9.21) .

Cyclization of the heterocyclic hydrazones 6, 7 and 13:

General procedure :

A solution of the appropriate hydrazone **6, 7** or **13** (1 mmol) in pyridine (10 ml) was refluxed for 3h, then left to cool. The solid that formed was filtered off, washed with ethanol and dried. Recrystallization from dimethylformamide afforded the corresponding fused-ring systems **8, 9** and **14**, respectively. ^1H NMR spectra were not obtained for these products due to their insolubility in the common NMR solvents.

8: Yield (84%); mp. 313-15°C; IR (KBr) ν 3351, 3199 (NH_2),1641 (C=O), 1611 (C=N) cm^{-1}; (Calcd. for $C_{19}H_{12}N_6OS$: C, 61.27; H, 3.24; N, 22.56; S, 8.60. Found : C, 61.15; H, 3.20; N, 22.27; S, 8.63) .

9: Yield (86%); mp. 309-11°C; IR (KBr) ν 3300, 3135 (NH_2), 1652 (C=O), 1607 (C=N) cm^{-1}; (Calcd. for $C_{12}H_7N_7OS$: C, 48.47; H, 2.37; N, 32.98; S, 10.78. Found : C, 48.33; H, 2.27; N, 32.70; S, 10.62) .

14 : Yield (76%); mp. 300-302°C; IR (KBr) ν 3300, 3142 (NH_2), 1640 (C=O), 1597 (C=N) cm^{-1}; MS, m/z (%) 346 (M^+, 96.6), 318 (50.0), 291 (21.1), 266 (58.6), 211 (33.6), 184 (22.8), 150 (53.4), 134 (90.1), 108 (63.8), 90 (84.1), 63 (61.2); (Calcd. for $C_{17}H_{10}N_6OS$: C, 58.94; H, 2.91; N, 24.26; S, 9.25. Found : C, 58.91; H, 2.95; N, 24.30; S, 9.18).

2-Arylhydrazono-3-(benzothiazol-2-yl)-3-oxopropanenitriles 16a-c.

General procedure:

To a stirred cold solution of 3-oxopropanenitrile **3** (4.04 g, 20 mmol) in ethanol (30 ml) and sodium acetate trihydrate (2 g), was added the appropriate arene diazonium chloride (20 mmol) portionwise over a period of 30 min at 0-5°C. After complete addition, the reaction mixture was stirred for further 3h at 0-5°C. The solid that precipitated was collected, washed with water and dried. Recrystallization from dimethylformamide afforded the corresponding hydrazones **16a-c.**

16a : Yield (85%); mp. 170-1°C; IR (KBr) ν 3250 (NH), 2225 (C≡N), 1700 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23-8.30 (m, 9H), 12.50 (br., 1H) ppm; (Calcd. for $C_{16}H_{10}N_4OS$: C, 62.72; H, 3.29; N, 18.29; S, 10.46. Found: C, 62.90; H, 3.32; N, 18.08; S, 10.55).

16b : Yield (98%); mp. 190-2°C; IR (KBr) ν 3250 (NH), 2225 (C≡N), 1665 (C=O), 1605 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 7.2-8.4 (m, 8H), 15.35 (br., 1H) ppm; (Calcd. for $C_{17}H_{12}N_4OS$: C, 63.74; H, 3.78; N, 16.66; S, 9.53. Found: C, 63.70; H, 3.72; N, 16.43; S, 9.60).

16c : Yield (98%); mp. 207-8°C; IR (KBr) ν 3210 (NH), 2218 (C≡N), 1665 (C=O), 1605 (C=N) cm^{-1}; (Calcd. for $C_{16}H_9ClN_4OS$: C, 56.39; H, 2.66; N, 16.44; S, 9.40. Found: C, 56.47; H, 2.80; N, 16.73; S, 9.32).

5-Amino-4-arylazo-3-(benzothiazol-2-yl)pyrazoles 17a-c and 18a-c.

General procedure :

To a solution of the appropriate hydrazone **16a-c** (5 mmol) in ethanol (20 ml) was added hydrazine hydrate or phenylhydrazine (5 mmol). The reaction mixture was refluxed for 1h, then cooled. The solid formed was collected, washed with ethanol, dried and finally recrystallized from DMF/H_2O to afford the corresponding 4-arylazopyrazole derivatives **17a-c** and **18a-c,** respectively.

17a : Yield (67%); mp. 267-8°C; IR (KBr) ν 3450, 3300, 3200 (NH_2, NH), 1620 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 7.28-8.30 (m, 9H), 11.93 (br., 2H), 13.25 (br., 1H) ppm; (Calcd. for $C_{16}H_{12}N_6S$: C, 59.99; H, 3.77; N, 26.24; S, 10.01. Found: C, 59.76; H, 3.80; N, 26.30; S, 10.07).

17b : Yield (66%); mp. 276-8°C; IR (KBr) ν 3460, 3300, 3210 (NH_2, NH), 1620 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 2.38 (s, 3H), 7.36-8.3 (m, 8H), 12.68 (br., 2H), 13.7 (br., 1H) ppm; (Calcd. for $C_{17}H_{14}N_6S$: C, 61.07; H, 4.22; N, 25.13; S, 9.57. Found: C, 60.88; H, 4.30; N, 25.10; S, 9.61).

17c : Yield (73%); mp. 294-6°C; IR (KBr) ν 3460, 3320, 3160, (NH_2, NH), 1620 (C=N) cm^{-1}; (Calcd. for $C_{16}H_{11}ClN_6S$: C, 54.16; H, 3.12; N, 23.69; S, 9.03. Found: C, 54.12; H, 3.28; N, 23.40; S, 8.79).

18a : Yield (62%); mp. 223-4°C; IR (KBr) ν 3465, 3300 (NH_2), 1620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.53 (br., 2H), 7.23-8.20 (m, 14H) ppm; (Calcd. for $C_{22}H_{16}N_6S$: C, 66.64; H, 4.07; N, 21.20; S, 8.08. Found:

C, 66.51; H, 3.88; N, 20.94; S, 8.20).

18b : Yield (65%); mp. 225-7°C; IR (KBr) ν 3478, 3310 (NH_2), 1620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.78 (br., 2H), 7.3-8.02 (m, 13H) ppm; (Calcd. for $C_{23}H_{18}N_6S$: C, 67.29; H, 4.42; N, 20.47; S, 7.81. Found: C, 67.50; H, 4.26; N, 20.23; S, 7.50).

18c : Yield (65%); mp. 236-7°C; IR (KBr) ν 3460, 3310 (NH_2), 1630 (C=N) cm^{-1}; (Calcd. for $C_{22}H_{15}ClN_6S$: C, 61.31; H, 3.51; N, 19.50; S, 7.44. Found: C, 61.07; H, 3.60; N, 19.21; S, 7.50).

5-Amino-3-(benzothiazol-2-yl)-1H-pyrazole 19 and 5-amino--3-(benzothiazol-2-yl)-1-phenylpyrazole 20:

General procedure:

A mixture of the 3-oxopropanenitrile **3** (4.04 g, 20 mmol) and hydrazine hydrate (1 ml, 80%) or phenylhydrazine (2 ml) in absolute ethanol (20 ml) was refluxed for 2-4h. The reaction mixture was allowed to cool and then diluted with water. The precipitated solid was collected, washed with water and dried. Recrystallization from ethanol afforded the pyrazoles **19** and **20**, respectively.

19 : Yield (73%); mp. 158-60°C; IR (KBr) ν 3410, 3340, 3180 (NH_2, NH), 1615 (C=N) cm^{-1}; (Calcd. for $C_{10}H_8N_4S$: C, 55.53; H, 3.72; N, 25.90; S, 14.82. Found: C, 55.38; H, 3.80; N, 25.74; S, 14.85).

20 : Yield (70%); mp. 171-2°C; IR (KBr) ν 3373, 3276 (NH_2), 1631 (C=N) cm^{-1}; (Calcd. for $C_{16}H_{12}N_4S$: C , 65.73; H, 4.14; N, 19.16; S, 10.96. Found: C, 65.95; H, 3.92; N,19.10, S, 10.58).

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